PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number: WO 94/00155
A61K 47/28	A1	(43) International Publication Date: 6 January 1994 (06.01.94)

(21) International Application Number: PCT/EP93/01508

(22) International Filing Date: 15 June 1993 (15.06.93)

(30) Priority data:
MI92A001601 30 June 1992 (30.06.92) IT

(71) Applicant *(for all designated States except US)*: MONTERESEARCH S.R.L. [IT/IT]; Via G. Galilei, 7, I-20016 Pero (IT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : BERLATI, Fabio [IT/IT]; CESCHEL, Giancarlo [IT/IT]; RODA, Aldo [IT/IT]; RODA, Enrico [IT/IT]; RONCHI, Celestino [IT/IT]; Via G. Galilei, 7, I-20016 Pero (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: THE USE OF NOR- AND HOMO- BILE ACIDS DERIVATIVES AS ABSORPTION ENHANCERS FOR MEDICAMENTS

(57) Abstract

The use of nor- and homo- bile acids derivatives as absorption enhancers for medicaments. Said derivatives show the advantage of improving the absorption of medicaments through mucosae without being metabolized by the intestinal flora, thus allowing a fast excretion. Moreover, the derivatives of the invention have a negligible toxicity.

FOR THE PURPOSES OF INFORMATION ONLY

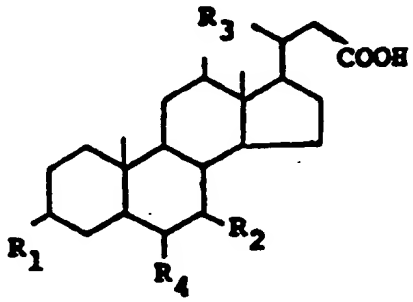
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovak Republic
SN	Senegal
TD	Chad
TG	Togo
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

THE USE OF NOR- AND HOMO- BILE ACIDS DERIVATIVES AS ABSORPTION ENHANCERS FOR MEDICAMENTS

The present invention relates to the use of nor- and homo- bile acids derivatives (hereinafter named NORAB and HOMOAB, respectively) as absorption enhancers for medicaments.

Particularly, the invention relates to the use of nor- and homo- bile acids derivatives having respectively the following formulae:



(I)

wherein:

	R_1	R_2	R_3	R_4
a)	α-OH	α-OH	H	H
b)	α-OH	β-OH	H	H
c)	α-OH	H	α-OH	H
d)	α-OH	H	β-OH	H
e)	α-OH	H	H	β-OH

corresponding to:

Ia) norchenodeoxycholic acid

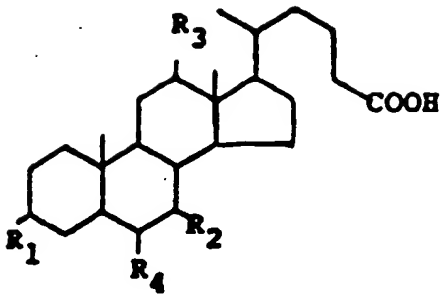
Ib) norursodeoxycholic acid

Ic) nordeoxycholic acid

Id) 24-nor-[3α,12β-dihydroxy-5β-cholan-23-oic] acid

Ie) 24-nor-[3α,6β-dihydroxy-5β-cholan-23-oic] acid

and



(II)

wherein:

	R_1	R_2	R_3	R_4
f)	α-OH	α-OH	H	H
g)	α-OH	β-OH	H	H
h)	α-OH	H	α-OH	H
i)	α-OH	H	β-OH	H
l)	α-OH	H	H	β-OH

corresponding to:

IIf) homochenodeoxycholic acid

IIg) homoursodeoxycholic acid

IIh) homodeoxycholic acid

IIi) 24-homo-[3α,12β-dihydroxy-5β-cholan-23-oic] acid

IIl) 24-homo[3α,6β-dihydroxy-5β-cholan-23-oic] acid.

It is also an object of the invention the use of the corresponding NORAB and HOMOAB conjugated respectively in C_{23} and C_{25} with taurine, glycine and alanine.

The present trend for pharmacological therapy, particularly in the case of slight disorders or of treatments involving multiple administrations repeated in time, and therapies for conscious patients, is the self-administration by the patient itself. From this point of view, the preferred administration routes are the enteral, i.e. buccal, rectal and intranasal ones.

The medicament administered through these routes,

once released from the pharmaceutic form containing it (tablet, suppository, aerosol, and the like), must cross the different mucosae coating the gastrointestinal tract and the nasal cavity, in order to enter the circulatory stream and be distributed in the various body districts thus reaching the action site.

Due to the complex nature of the mucosae and the different chemical structure of the medicaments, the crossing of the mucosae involves different difficulties, depending on the kind of medicament and the type of mucosa.

One of the main problems involved in the design of medicaments consists in the need to give the pharmacologically active compound those hydrophilic characteristics which are generally required to have the active principle dissolved in the biological liquids (serum, interstitial liquid) and sometimes also lipophilic characteristics to cross the mucosa, which generally consists of a more or less complex cell barrier.

This approach finds a number of difficulties from the viewpoint of the medicament design, both in the synthesis and in the pharmacokinetic expectation.

A different approach to this problem consists in combining the active principle with a compound enhancing the absorption of the medicament through the mucosa.

Due to the single chemico-physical peculiarities of the different medicaments, up to now it was necessary to look for absorption enhancers suitable for both the considered medicament and the involved mucosa.

Bile acids (BA) are natural detergents capable of

forming, with other poorly water-soluble medicaments, mixed micells with phospholipids and cholesterol at a relatively low concentration (1-4 mM).

Moreover, thanks to the structure thereof, they are also relatively lipophilic (log p = 2 ÷ 4) and therefore they can passively cross the biologic membranes. The bile acids crossing and partitioning in the lipidic domain exert their activity in this microenvironment modifying the cholesterol content and therefore increasing the permeability to other substances.

A bile acid designed to be an enhancer, moreover, must be:

1) relatively lipophilic, with a partition coefficient octanol/water log P $\geq$ 1;
2) relatively detergent, with a critical micell concentration $\leq$ 7 ± 2 mM;
3) stable to intestinal bacterial flora and particularly not 7-dehydroxylated and oxidized to potentially toxic or inactive compounds.

Now it has been found that bile acids derivatives in which the side chain has one carbon atom more (NOR) or one less (HOMO) proved remarkable properties as absorption enhancers for medicaments by the enteral route and other not-parenteral routes (intranasal, buccal, sublingual).

Particularly, the best results were obtained with derivatives of the dehydroxylated bile acids above reported with two OH at the 3α7α, 3α7β, 3α6α, 3α12α and 3α12β positions. The choice of one of the above reported epimers will depend on the substance to carry.

Compared with the natural derivatives, the nor- and homo-derivatives show the advantage that they are not metabolized by the intestinal bacterial flora and have a very high stability in anaerobic and aerobic fecal culture.

The change in the side chain can prevent a 7 dehydroxylation of the 3α7α and 3α7β derivatives with an enormous advantage compared with the natural components which are quickly metabolized.

The glycine- or taurine- amidated compounds also show a high stability to bacterial flora compared with physiological bile acids (BA) which are quickly deconjugated.

The derivatives of the invention are useful as absorption enhancers for medicaments administered by the enteral route or by other routes (intranasal, buccal, sublingual).

One of the most preferred administration routes is the rectal one, since these compounds are absorbed by the rectal mucosa and, once in circulation, the are immediately transformed into glucuronide derivatives at the hepatic level and excreted through the feces (even though they are not metabolized by the bacteria in the last intestinal tract, as already mentioned).

The general toxicity thereof is negligible even at doses 100 times higher than the envisaged ones.

The compounds of the invention can be obtained semisynthetically according to known methods.

The medicaments which can be advantageously combined with iodeoxycholic acid belong in various chemical and/or therapeutical classes, such as

peptides, not steroidal antiinflammatories, steroids, diuretics, cardiovasculars, hormones, local anaesthetics, antihistaminics, rhinologic and anticolinergic agents.

NORAB and HOMOAB, compared with the up to now known enhancers, particularly with other bile acids previously used (cholic and taurocholic acids) show the following advantages:

- higher effectiveness;
- lower toxicity;
- metabolic stability towards the bacterial flora responsible for undesired biotransformations, such as the conversion of taurocholic acid into deoxycholic acid;
- optimum lipohilia for the increase in cell membrane permeability, thanks to the capability of forming reverse micells inside which a part of membrane cholesterol dissolves, thereby the membrane becoming more permeable;
- low detergency, which therefore causes no damages nor inflammations.

Examples of rectal formulations according to the invention comprise suppositories, microclysmas, soft gelatin rectal capsules.

For the intranasal administration, sterile solutions or powders are suitable, whereas oral or buccal forms comprise capsules, tablets, bioadhesive tablets and the like.

The preparation techniques and the excipients used for the preparation of said pharmaceutical forms are the conventional ones known, for example, from

Remington's Pharmaceutical Sciences, Mack Pub., Co., N.Y., USA, XVII Ed.

For the oral use, the presence of NORAB and/or HOMOAB enhances the absorption of some active principles such as NSADs, diuretics and the like.

For the oral administration, the action of the derivatives of the invention takes place mainly at the duodenal and intestinal levels, therefore, in order to optimize the absorption, gastroresistant forms or controlled-release forms are preferably used, allowing the tablet to disintegrate at well-controlled pH values which are characteristic of a particular portion of the intestinal tract.

According to the invention, NORABs and HOMOABs are used in amounts from 0.1 to 100 mg per unitary dose. Preferably, for the oral, buccal and rectal forms, they are present in amounts from 10 to 40 mg per unitary dose, whereas for intranasal forms they range from 0.5 to 10 mg per unitary dose.

The following examples further illustrate the invention. In said examples, Enhancer HOMOAB1, Enhancer NORAB1, Enhancer HOMOAB2, Enhancer NORAB2, Enhancer HOMOAB3, Enhancer NORAB4, Enhancer HOMOAB5 and Enhancer NORAB5 means, respectively, the following acids: homochenodeoxycholic, norchenodeoxycholic, homoursodeoxycholic, norursodeoxycholic, homodeoxycholic, 24-nor-[3α,12β-dihydroxy-5β-cholan-23-oic], 24-homo-[3α-6β-dihydroxy-5β-cholan-23-oic] and 24-nor[3α-6β-dihydroxy-5β-cholan-23-oic].

EXAMPLE 1

Diclofenac suppositories

One suppository contains:

Sodium diclofenac		100 mg
Enhancer HOMOAB1		20 mg
Whitepsol H 15	q.s. to	2,5 g

EXAMPLE 2

Calcitonin rectal capsules

One soft gelatin capsule for rectal use contains:

Synthetic salmon calcitonin		100 I.U.
Enhancer NORAB1		20 mg
Vaseline oil	q.s. to	700 mg

EXAMPLE 3

Dipyrone coated tablets

One coated tablet contains:

Dipyrone	250 mg
Starch	125 mg
Enhancer HOMOAB2	100 mg
Microcrystalline cellulose	150 mg
Talc	30 mg
Magnesium stearate	20 mg
PVP K30	30 mg
Methacrylic acid polymer	10 mg
Diethyl phthalate	0,5 mg

EXAMPLE 4

Furosemide tablets

One tablet contains:

Furosemide	20 mg
Enhancer NORAB2	20 mg
Starch	50 mg
Lactose	50 mg
PVP K30	3 mg

Talc		1 mg
Magnesium stearate		1 mg
Croscaramellose		5 mg

EXAMPLE 5

Metronidazole tablets

One tablet contains:

Metronidazole	250 mg
Microcrystalline cellulose	200 mg
Starch	130 mg
Enhancer HOMOAB3	100 mg
Talc	10 mg
Sodium amidoglycolate	100 mg

EXAMPLE 6

LHRH for buccal use:

One administration unit contains:

LHRH	50 mcg
Starch	80 mg
Carboxyvinyl polymer	100 mg
Enhancer NORAB4	20 mg

EXAMPLE 7

LHRH for intranasal administration:

One administration unit contains:

LHRH		50 mcg
Enhancer HOMOAB5		5 mg
Mannite	q.s. to	20 mg

EXAMPLE 8

GRH for intranasal administration:

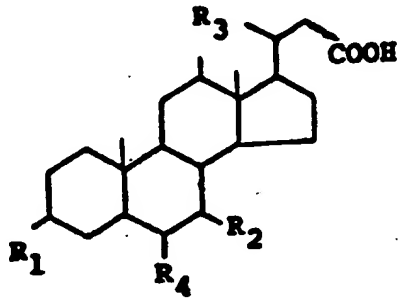
One administration unit contains:

GRH		50 mcg
Enhancer NORAB5		2,5 mg
Mannite	q.s. to	20 mg

CLAIMS

1. The use of nor- and homo- bile acids derivatives and of the conjugated thereof in C_{23} and C_{25} with taurine, glycine and alanine as absorption enhancers for medicaments.

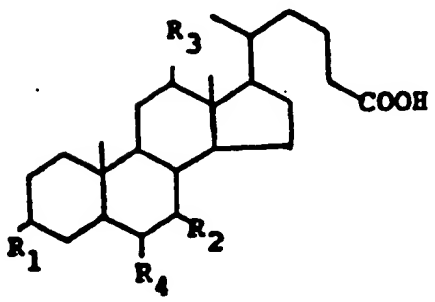
2. The use of nor- and homo- bile acids derivatives and of the conjugated thereof in C_{23} and C_{25} with taurine, glycine and alanine, having the following formulae:



(I)

wherein:

	R_1	R_2	R_3	R_4
a)	α-OH	α-OH	H	H
b)	α-OH	β-OH	H	H
c)	α-OH	H	α-OH	H
d)	α-OH	H	β-OH	H
e)	α-OH	H	H	β-OH



(II)

wherein:

	R_1	R_2	R_3	R_4
f)	α-OH	α-OH	H	H
g)	α-OH	β-OH	H	H
h)	α-OH	H	α-OH	H
i)	α-OH	H	β-OH	H
l)	α-OH	H	H	β-OH

as absorption enhancers for medicaments.

3. The use according to claims 1-2, characterized in that the absorption takes place in the gastrointestinal tract.

4. The use according to claim 3, characterized in that the absorption takes place at the buccal mucosa level.

5. The use according to claim 3, characterized in that the absorption takes place in the duodenal tract.

6. The use according to claim 3, characterized in that the absorption takes place in the intestinal tract.

7. The use according to claim 3, characterized in that the absorption takes place in the rectal tract.

8. The use according to claims 1-2, characterized in that the absorption takes place in the intranasal cavity.

9. The use according to claims 1-8, characterized in that the medicaments are selected from peptides, not steroidal antiinflammatories, steroids, diuretics, cardiovasculars, hormones, local anaesthetics, antihistaminics, rhinologics, anticolinergics.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01508

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K47/28

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 135 782 (LEHNER A.G.) 3 April 1985 see claims see page 1, line 20 - line 24 see page 2, line 19 - line 21 see page 12, line 4 - line 14	1-9
A	EP,A,0 128 831 (M.C.CAREY) 19 December 1984 see claims	1-9

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 SEPTEMBER 1993	30.09.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9301508
SA 76009

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 22/09/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0135782	03-04-85	JP-B- 1044197	26-09-89
		JP-C- 1561393	31-05-90
		JP-A- 60075495	27-04-85
		US-A- 4981983	01-01-91
EP-A-0128831	19-12-84	US-A- 4548922	22-10-85
		US-A- 4746508	24-05-88
		AU-A- 2902084	13-12-84
		AU-A- 3256189	03-08-89
		CA-A- 1228298	20-10-87
		DE-A- 3486028	18-02-93
		JP-A- 61033126	17-02-86
		US-A- 4959358	25-09-90